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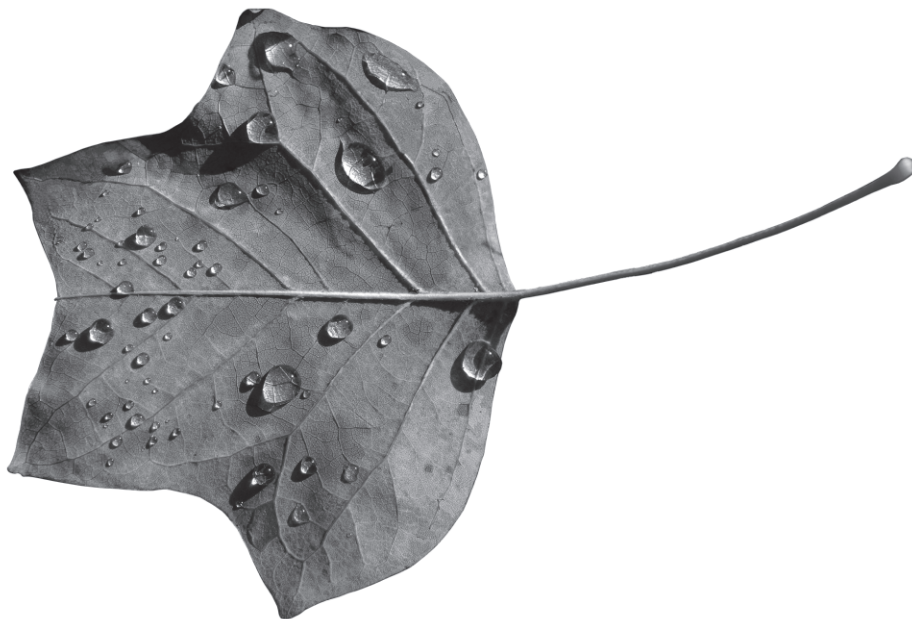
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Part I

General introduction



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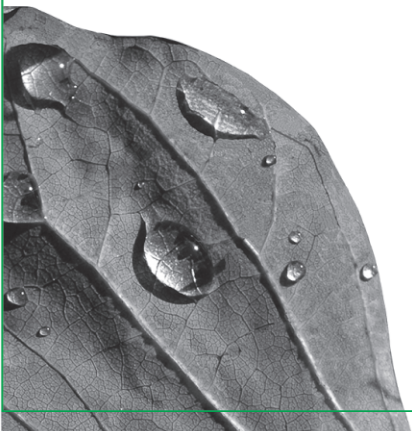
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General introduction, aims & outline

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General Introduction

Historically, the focus of neuroscience has been on localizing different functions in the brain. A classical example of this approach is the identification of the motor speech center, located in the ventroposterior region of the left frontal cortex, by the French neurologist Paul Broca during the last decades of the 19th century (Dronkers et al., 2007). This approach has led to a substantial increase in knowledge about information processing in segregated brain areas, whereas an understanding of how these regions communicate to establish higher-level brain processes was still lacking. During the past decades the knowledge about these processes has increased, as evidence has accumulated that neural networks throughout the brain are a fundamental condition for the integration between brain regions. There is increasing support for the idea that the brain should be conceived as a large complex network of interconnected elements at multiple scales (at structural level e.g. neurons, white matter tracts, but also on a functional level where communication between (remote) brain regions amongst others takes place through synchronization) (Varela et al., 2001; Fries, 2005; Uhlhaas and Singer, 2006; Hagmann et al., 2007; Stam and van Straaten, 2012b). Both the spatial and the temporal patterns of the interactions are important characteristics to increase the understanding of the underlying anatomical and functional networks, and contribute to the knowledge of brain function and dysfunction (Bassett et al., 2008; Bullmore and Sporns, 2009).

In neurophysiology we focus on brain function. The function of the brain is studied by recording the summated excitatory (and inhibitory) post-synaptic potentials (EPSP and IPSP) of the (pyramidal) neurons in columns situated in the cortex, with electroencephalography (EEG) or magneto-electroencephalography (MEG). The recorded electrical signals form a set of time series. Statistical interdependency (synchronization) between these time series is assumed to reflect the interaction between different (remote) brain areas. Functional connectivity refers to the existence of any statistical interdependency between time series and was first introduced by Aertsen and others (1989), whereas effective connectivity stresses the asymmetric causal interactions between brain regions (Friston, 2002). Balanced connectivity is very important for normal functioning of the brain and can be quantified by both linear and nonlinear measures (Pereda et al., 2005). Previous work has shown that brain diseases such as Alzheimer's disease, schizophrenia, brain tumors, and epilepsy affect functional connectivity and the functional network architecture (Bartolomei et al., 2006a; Ponten et al., 2007; de Haan et al., 2009; van den Heuvel et al., 2010). In this thesis we will estimate functional connectivity between brain regions in EEG recordings of epilepsy patients, and construct functional brain networks to study epileptic seizures.

Epilepsy

Epilepsy is the world's most prevalent brain disorder affecting approximately 1% of the world's population (Litt and Echauz, 2002). It is defined as the condition of recurrent

unprovoked epileptic seizures and can have a wide variety of underlying causes (Duncan et al., 2006). One of the most disabling aspects of epilepsy is the unpredictable way in which seizures occur (Hauser et al., 1993). Despite enormous research efforts, the underlying mechanisms of epileptic seizures are still poorly understood (Timofeev and Steriade, 2004). Most of the research focuses on molecular, anatomical, and cellular physiological mechanisms both involved in the development of epilepsy and the initiation of seizures. As described above, synchronization of neurons is important for normal functioning of the brain, in particular for information processing. The most widely accepted concept in epileptogenesis is that an abnormal hypersynchronization of firing activity of neurons, combined with abnormal communication between brain regions, can cause seizure activity (Penfield and Jasper, 1954; Lehnertz et al., 2009).

About a decade ago, one of the most intensely studied epilepsy-research topics was the prediction of seizures in EEG recordings, for example by calculating the synchronization strength from the interictal towards the pre-ictal and ictal state, or by analyzing (changes in) the nonlinear components in EEG signals (Babloyantz and Destexhe, 1986; Iasemidis et al., 1990; Mormann et al., 2003; Le Van Quyen et al., 2005; Wendling et al., 2005). Surprisingly, both increases and decreases in synchronization have been found in the EEG recording directly preceding seizure activity (called the pre-ictal state) compared to recordings long before or after seizures (the interictal state) (Mormann et al., 2003; Le Van Quyen et al., 2005). Other studies have shown that the highest level of synchronization in partial seizures might be reached only at the very end of the seizure (Schindler et al., 2007). Overall, it can be concluded that the before-mentioned hypersynchronization concept is an oversimplification of the processes that occur preceding and during seizures (Netoff et al., 2004; Wendling et al., 2005). Despite the limitations of this concept, it has been shown (Ferri et al., 2004; Slooter et al., 2006) that epileptic seizures can be distinguished from interictal activity by calculating the synchronization likelihood (SL), a measure of nonlinear interdependencies between time series (Stam and van Dijk, 2002). In these studies the SL was higher during seizure activity.

Recently, the focus of epilepsy research has shifted in the direction of graph theoretical analysis, applied to functional brain networks. This type of analysis has offered new perspectives and insights into the nature of epilepsy (Kramer and Cash, 2012; van Diessen et al., 2013a). Some interesting topics in this context are the characterization of the functional network topology before and during seizure activity (some of these studies are described in this thesis), the identification of epileptogenic zones to improve seizure freedom after epilepsy surgery, and the identification of diagnostic tools for epilepsy (Ortega et al., 2008; Douw et al., 2010; van Diessen et al., 2013b).

EEG in the intensive care unit (ICU)

Continuous EEG monitoring (cEEG) has been introduced as a potentially valuable monitoring technique for brain function. Even with recommendations in the

literature, facilities for monitoring brain function are missing in most ICU's, despite the high complication rate in comatose neurological patients (Vespa et al., 1999a; Claassen and Mayer, 2002; Hirsch, 2004; Friedman et al., 2009). Moreover, it has also been shown that cEEG could contribute to medical decision-making in the ICU (Jordan, 1993). Another important application of cEEG in the ICU is the detection and follow-up of (non-convulsive) seizures and status epilepticus, as seizures appear to be frequent in these critically ill patients (Towne et al., 2000; Claassen et al., 2004; Oddo et al., 2007). Although cEEG is used more often nowadays, an online detection device to recognize seizure activity is still missing. In a successful first attempt, using overall functional connectivity levels in EEG recordings, seizure activity was recognized in both adult ICU patients and neonates, where seizures were characterized by a higher level of functional connectivity (Altenburg et al., 2003; Slooter et al., 2006).

The classification of (non-convulsive) seizures in ICU patients still depends on the visual inspection of their EEG recordings. There is only one set of criteria available to support the interpretation of non-convulsive seizures in critically ill ICU patients (Young et al., 1996), revised by Chong and Hirsch (2005). Besides the difficult recognition of seizure activity, there is also a problem in interpreting generalized (or lateralized) periodic discharges. These EEG patterns occur frequently in critically ill patients (Hirsch et al., 2005), yet there is controversy regarding the epileptic origin and therapeutic implications of these periodic patterns in critically ill patients. This is illustrated by the fact that periodic discharges have been interpreted as interictal, ictal and postictal activity (Pohlmann-Eden et al., 1996; Brenner, 2002; Rossetti et al., 2007). Anti-epileptic drug treatment can improve the outcome in patients suffering seizures, but can also have significant side effects. To give critically ill ICU patients the most optimal medical treatment, more insight in the emergence of periodic EEG patterns and their relation to seizure activity is certainly needed (Tjepkema-Cloostermans et al., 2013). In this thesis we will explore the use of functional connectivity and modern network theory in EEG recordings from critically ill ICU patients to investigate the relation between periodic EEG patterns and seizure activity.

Modern network theory

The brain can be considered as a complex structural and functional network (Bullmore and Sporns, 2012). Application of network theory certainly is a promising approach to understand this complex nature of the brain (Rubinov and Sporns, 2010). This approach can only be successful though when the extensive knowledge of other scientific fields that deal with complex systems, such as the science of dynamical systems and statistical physics, is also taken into account (Stam and van Straaten, 2012b). The experience with deterministic and nonlinear systems contributes to our understanding of the complex, often nonlinear, behavior of the brain (Stam, 2005). Many nonlinear methods to estimate synchronization processes between neurons and brain regions have been developed (Boccaletti et al., 2006). For instance,

concepts derived from nonlinear dynamics have been applied extensively to study the predictability of seizures in EEG recordings (Mormann et al., 2007). Phase transition, a concept used in statistical physics, has also been introduced in neuroscience. In statistical physics it has been observed that complex systems evolve towards phase transitions in a critical state, which are characterized by power laws (Bak et al., 1987). Similarly, the sudden transition from interictal brain activity towards seizure activity is probably also a kind of phase transition (Lopes da Silva et al., 2003a).

Modern network theory is based on graph theory, a relatively old branch of mathematics. Leonhard Euler laid the foundations for graph theory, with his attempt to solve the problem of the famous seven bridges of Königsberg (Euler, 1741). Originally, graph theory dealt with relatively small networks represented as graphs consisting of nodes (or vertices) and connections between nodes (also called edges). Connections between nodes either exist or not exist, but one can also assign a weight to an edge that reflects for instance the strength of the relation between the two nodes. In the first setting one speaks of unweighted graphs, in which an arbitrary threshold is used to determine if an edge exists; in the second scenario weighted graphs are formed. Besides, edges can be directed or undirected, where in directed edges information of the direction of the information flow is given. With the introduction of models that unify descriptions and analyses of large networks, the use of graphs has expanded enormously, and modern network theory is nowadays used to characterize a large variety of complex networks. The first example of such a model is the random graph model proposed by Erdős and Rényi (1960).

Early random graph models like the ER model, have limitations in simulating complex networks; as for instance the high local clustering, as observed in real networks, can not be explained by this model. At the end of the 20th century two scientific papers have given graph theory another boost by introducing new statistical approaches to networks, respectively the rewiring probability of edges in networks, and the application of network growth (Watts and Strogatz, 1998; Barabasi and Albert, 1999). Watts and Strogatz presented the small-world concept. They used a simple one-dimensional model of a regular graph on a ring, in which edges are rewired randomly, with a probability p . In between regular graphs (characterized by a high local connectedness or clustering coefficient C , and a long path length L , which means that it takes on average many steps to travel from a node to another node in the network), and random graphs (characterized by low C and short L), small-world networks appeared, characterized by a high C and a low L (Watts and Strogatz, 1998). Human brain networks, both structural and functional, have been shown to have small-world properties (Eguiluz et al., 2005; He et al., 2007).

Barabasi and Albert described a growth algorithm ('preferential attachment') to generate scale-free networks, where newly added nodes connect preferentially to existing nodes that have many connections (Barabasi and Albert, 1999). This model explained the appearance of nodes with an exceptional high number of connections

and a scale-free degree distribution. Other important characteristics of many complex networks are the presence of smaller functional sub-groups, called ‘motifs’ of the network, or the relative node importance, captured by measures that quantify the centrality of a node. These include among others the degree of a node (the number of connections with other nodes), the betweenness centrality (Wang et al., 2008), and the eigenvector centrality (de Haan et al., 2012b). A recent overview is given by Bullmore and Sporns (2012).

Graphs can be constructed from all kind of networks, e.g. social networks, public transport networks, networks of individual neurons or brain regions. Despite the advantages of applying network theory in neuroscience, the optimal way to construct networks and to compare different networks is still unknown. Therefore, the minimum spanning tree (MST) has been introduced recently to neuroscience in order to describe the functional backbone of a network (Lee et al., 2006; Wang et al., 2008; Boersma et al., 2013). The MST is a unique sub-graph of the undirected weighted graph, which connects all nodes in such a way that the functional wiring cost (sum of all link distances) is minimized without forming loops, containing N nodes (the same as the original graph) and $M = N-1$ edges. This enables direct comparison of the MSTs between groups and avoids methodological biases as for instance the MST does not need an arbitrary threshold (Van Mieghem and van Langen, 2005; van Wijk et al., 2010).

Aims of the thesis

The underlying processes of seizures are still a mystery. Seizures appear in many different brain diseases, and can be an expression of localized lesions, often with a disturbed balance between excitation and inhibition (e.g. mesial temporal sclerosis, brain tumors), the result of a more global dysfunction (e.g. post-anoxic encephalopathy), or part of a great variety of genetic disorders. The general aim of this thesis is therefore to apply functional connectivity and functional brain network analysis to increase our knowledge of seizure activity, mainly in critically ill patients admitted to the intensive care unit (ICU). Different perspectives are used to approach our general aim, leading towards the following hypotheses:

EEG in the intensive care unit

- The synchronization likelihood (SL) is sensitive to detect epileptic seizures in the ICU and can be used to implement an online seizure detection device.
- The gold standard of non-convulsive seizure recognition in the ICU, namely the visual interpretation of the EEG recording, is not very reliable.

Network analysis in seizures and periodic discharges

- Using network analysis, seizure characteristics might be equally in different seizure types.
- Generalized periodic discharges can be interpreted as a state beyond seizure activity using functional connectivity and network analysis.

Neural mass models combined with network analysis

- The underlying structural network architecture can not forecast the associated functional network properties in complex networks.
- Neural mass models can be useful to investigate the emergence of EEG patterns in neurological patients.

Outline of the thesis

Part 1 Introduction

Modern network theory is offering an increasing number of measures to study complex networks in the brain and it is still a fast developing field in neuroscience. **Chapter 2** gives a detailed overview of the application of modern network analysis to neuroscience. The historical background and basic principles of graph theoretical analysis are offered. This is followed by examples of its application in both experimental neuroscience (neuroanatomical and neurophysiological), and in patients with disturbed brain function (e.g. cognitive disturbances, epilepsy and psychiatric disorders), where it has been used to expand the knowledge of the pathophysiological mechanisms.

Part 2 EEG recordings in the intensive care unit

This part focuses on critically ill ICU patients. Despite the fact that clinical neurophysiologists are involved, almost on a daily basis, with the assessment of brain function in comatose patients, they are still struggling with the visual interpretation of their EEG recordings. Previous studies have described a high prevalence (8-19%) of epileptic seizures occurring in ICU patients, and they have often recommended continuous EEG monitoring (cEEG) in the ICU (Vespa et al., 1999a; Towne et al., 2000; Claassen et al., 2004; van Putten and Tavy, 2004; Cloostermans et al., 2011). Other studies have demonstrated the accuracy of SL in detecting seizures of various types, including seizures occurring in critically ill patients (Altenburg et al., 2003; Ferri et al., 2004; Slooter et al., 2006). **Chapter 3** describes a prospective, descriptive study we performed to implement cEEG monitoring, including a device for online seizure detection in the ICU. This device is based on the concept of hypersynchronization of neural activity during seizures and uses the SL to detect changes in synchronization levels. The verification of the accuracy of this device is the visual interpretation of the EEG recordings, which is the gold standard for seizure activity in ICU patients (Young et al., 1996; Hirsch et al., 2005). In **chapter 4** we assess the reliability of the visual inspection of EEG recordings registered in the ICU. A group of (in)-experienced neurophysiologists evaluated EEG recordings of ICU patients in a controlled way, and we calculated their agreement (i.e. the inter-rater variability) in terms of identification of seizure activity.

Part 3 Graph theoretical analyses of seizure activity

Part 3 describes graph theoretical network analysis of seizure activity for different seizure-types. **Chapter 5** contains our retrospective study with intracranial EEG

recordings of mesial temporal lobe epilepsy patients, exploring whether there are changes in synchronization between brain regions (functional connectivity) and in functional neural network topology during seizures. Without considering a previously published case study, this is the first study where network analysis was applied to intra-cerebral recordings of epileptic seizures. For further exploration of the application of network analysis to recordings of seizure activity, we performed the study described in **Chapter 6**. It introduces functional network analysis applied to surface EEG recordings of absence seizures. We evaluated the hypothesis that comparable changes in the functional neural network occur during this generalized seizure type as found during temporal seizures. We also explored the application of network analysis in surface EEG recordings in order to distinguish seizure activity from interictal patterns. **Chapter 7** addresses the clinical question whether or not generalized periodic discharges in critically ill patients should be considered as a kind of seizure activity. We used functional connectivity, followed by network analysis, and the construction of the minimum spanning tree (MST).

Part 4 Neural mass model

Modern network theories can be applied to functional neural networks (EEG, MEG and fMRI) as well as to structural neural networks (e.g. based on white matter tracks estimated from diffusion tensor imaging (DTI)). The relationship between structural and functional networks is still under debate; it is evident that functional networks must be related to structural networks, but it also clear that there is no direct one-to-one mapping (Honey et al., 2009). **Chapter 8** explores in a combined neural mass model (NMM) and graph theoretical model the relationship between structural network properties and both functional connectivity and functional network properties. Finally, **chapter 9** speculates on the impact for encephalopathy of this new combined NMM model approach, and presents some preliminary findings.

Part 5 Summary, general discussion, and future directions

In this final part, the results and methodological issues of the previous parts are summarized and discussed. Furthermore, a prospective view for future investigation is given.

